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Pharmacokinetics of [^{14}C]Teicoplanin in Male Rats after Single Intravenous Dose

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The pharmacokinetic profile of [^{14}C]teicoplanin was studied in male Sprague-Dawley rats given a single 10,000-U/kg intravenous dose. The disposition of the antimicrobial activity in the body was estimated by a three-compartment open model. Plasma concentration data were fitted to a three-exponent equation. The profile of total ^{14}C in plasma was similar to that of the microbiological activity. The cumulative recovery of total ^{14}C 5 days after drug administration averaged 76.3% of the administered dose in the urine and 8.7% in the feces. The residual dose remaining in the animal carcasses was 11.1%. Teicoplanin was widely distributed in the body. In almost all organs, the maximum concentration of [^{14}C]teicoplanin was already reached at the first time of killing, which was 0.25 h after the administration of drug. The liver, kidneys, skin, and fat contained most of the residual dose found in the animal carcasses 120 h after administration and behaved as a deep compartment with the adrenal glands and spleen.

Teicoplanin (teichomycin) is a new glycopeptide antibiotic produced by *Actinoplanes teichomyceticus* sp. nov. and is chemically related to the vancomycin-ristocetin group of antibiotics (1, 10). Teicoplanin is a mixture of closely related components (2, 4) that are active against gram-positive aerobic and anaerobic bacteria (5, 9, 10). Teicoplanin blocks bacterial cell wall synthesis by inhibiting the terminal process of peptidoglycan polymerization (12); therefore, it is bactericidal for growing microorganisms (9).

The antibiotic can be given intramuscularly as well as intravenously (3, 14). The purpose of this investigation with teicoplanin administered intravenously to rats was to determine its profile in blood, the recovery of the administered dose in excreta, and its distribution and rates of washout from selected organs and tissues by using radiochemical and microbiological assay methods.

MATERIALS AND METHODS

Experimental design. A single 10,000-U/kg intravenous dose of [^{14}C]teicoplanin was given to male Sprague-Dawley rats. (One unit of activity [U] is defined as that amount of activity contained in 1 μg of pure teicoplanin. The [^{14}C]teicoplanin administered to rats [diluted 1:1 with unlabeled teicoplanin] had a potency of 815 U/mg.) The volume of administration was 1 ml/kg. The rats (weight, 150 to 200 g) were acclimatized for 5 days in a temperature- and humidity-controlled room before treatment and were given the antibiotic after an overnight fast. The rats had free access to water. Food (standard diet 4 RF 21; Charles River Breeding Laboratories, Italiana Mangimi, Settimo Milanese, Italy) was offered 4 h after the administration of drug.

(i) Plasma kinetics. Under light ether anesthesia, blood samples were collected with heparinized pipettes, and plasma was separated by centrifugation at 1,500 × *g* at room temperature.

(ii) Recovery of teicoplanin. Exhaled CO_2 was trapped in Carbo-Sorb (Packard Instrument Co., Inc., Downer Grove, Ill.) for 48 h. Urine and fecal samples were collected for 120 h. Feces were placed into three times their weight of 0.1 M phosphate buffer (pH 7.4) and homogenized. Five days after drug administration, the animals were killed, cut into pieces, and homogenized in three times their weight of 0.1 M phosphate buffer (pH 7.4).

(iii) Tissue distribution. The distribution of [^{14}C]teicoplanin was studied at intervals of 0.25, 4, 24, 48, 72, and 120 h after the injection of drug. The animals were dissected immediately after exsanguination from the abdominal aorta. Selected organs and tissues were removed; lighty washed with 0.9% saline to remove blood, urine, and bile; wiped on blotting paper; placed into different volumes of 0.1 M phosphate buffer (pH 7.4), depending on the tissue, to obtain samples of satisfactory volume and fluidity; homogenized with a Polytron homogenizer (model PT 10-35; S. Kinematica GmbH, Lucerne, Switzerland); and freeze-dried.

Chemicals. [^{14}C]teicoplanin (specific activity, 2.28 μCi/mg) was obtained biosynthetically by fermentation of *A. teichomyceticus* sp. nov., using uniformly labeled [^{14}C]tyrosine as a precursor.

The high-pressure liquid chromatographic analysis of [^{14}C]teicoplanin by UV and radiochemical detection showed that the compound had a high radiochemical purity (99.0%) and that incorporation of ^{14}C in each fraction of the teicoplanin complex was uniform. The microbiological activity was 750.3 U/mg. The radioactive material was diluted 1:1 (U/U) with unlabeled teicoplanin, the microbiological activity of which was 894 U/mg. The diluted radioactive material was dissolved in aqueous 0.05 M $NaHCO_3$ at a concentration of 10,000 U/ml. Solutions were made up immediately before administration and used within 1 h of preparation.

Radiochemical assay. Immediately after collection, the radioactivity was measured by liquid scintillation counting (LSC) in plasma, urine, and the CO_2 absorber Carbo-Sorb after the addition of Insta-Gel (Packard) as the scintillation cocktail (10 ml). Blood samples were dissolved in a 1:1 mixture of Soluene-350 (Packard)–isopropyl alcohol (1.5 ml) and treated with 30% H_2O_2 (0.5 ml). Counts were made by LSC 1 h after the addition of a 9:1 mixture of Insta-Gel–0.5 N HCl (15 ml). Homogenized and freeze-dried tissue and total animal carcass samples were rehydrated and dissolved

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TABLE 1. Concentrations of teicoplanin in plasma determined by radiochemical and microbiological assay[a]

Assay	Concn (U/ml) at the following times (h):										
	0.05	1	2	4	8	12	24	36	48	60	72
^{14}C	121.47 ± 4.60	35.43 ± 0.90	23.28 ± 0.29	14.89 ± 0.44	6.21 ± 0.16	3.14 ± 0.08	0.81 ± 0.02	0.34 ± 0.04	0.20 ± 0.01	0.16 ± 0.01	0.12 ± 0.00
Microbiological	95.6 ± 6.6	27.2 ± 0.6	17.4 ± 1.0	10.4 ± 0.6	3.5 ± 0.1	1.6 ± 0.0	0.5 ± 0.0	0.2 ± 0.0	ND[b]	ND	ND

[a] Values are mean ± standard error (n = 4).
[b] ND, Not detectable.

in a 5:1 mixture of Soluene-350–isopropyl alcohol (1 ml), treated with 30% H_2O_2 (0.5 ml), and warmed at 50°C for 4 h. Counts were made after Dimilume 30 (15 ml; Packard) was added as the scintillation cocktail. Freeze-dried fecal samples were rehydrated, dissolved in Soluene-350 (1 ml), and kept at 50°C for 2 h; then, isopropyl alcohol (0.5 ml) and 30% H_2O_2 (0.2 ml) were added, and the samples were incubated at 50°C for an additional 2 h. Counts were made after water (4 ml) and Dimilume 30 (10 ml) were added. All the measurements were made with a liquid scintillation spectrometer (Tri-Carb; model 3255; Packard).

Microbiological assay. The antibacterial activity was measured in plasma, urine, and feces and tissue homogenates by an agar diffusion method with *Bacillus subtilis* ATCC 6633 as the test organism, incubation at 37°C overnight, and a three by three randomized block design. Nine 6-mm wells were dug in 12-cm-diameter plates filled with 12 ml of AM2 (USP)–6% NaCl (pH 6.6) medium, supplemented with 5% (vol/vol) 1 M KH_2PO_4, and inoculated with 0.5% (vol/vol) of a suspension of spores (1.5×10^8/ml) in sterile distilled water. A stock solution of standard teicoplanin was prepared at a concentration of 10 U/ml in 0.1 M phosphate buffer (pH 7.4) from which the three applied concentrations of 0.1, 0.2, and 0.4 U/ml were prepared with either bovine serum (for blood and plasma samples) or 0.1 M phosphate buffer (pH 7.4; for urine, tissue homogenates, and feces) used as a diluent. After a preliminary assay, the samples were diluted approximately to 0.1, 0.2, and 0.4 U/ml with the same diluent used for the appropriate standard, thus minimizing possible matrix interferences. The limit of detection of the method was 0.05 U/ml, and its precision was ±5% for sample concentrations ranging from 0.2 to 500 U/ml.

Data analysis. Levels of total ^{14}C and antimicrobial activity in plasma were fitted to the following three-exponent equations: $C_p = A_1 e^{-\lambda_1 t} + A_2 e^{-\lambda_2 t} + A_3 e^{-\lambda_3 t}$, in which C_p is the concentration in plasma at time t, A_n are hybrid coefficients, and λ_n are hybrid first-order rate constants.

The following kinetic parameters were measured or calculated (6) for total radioactivity, antimicrobial activity, or both: peak level (C_{max}); hybrid first-order rate constants (λ_n); hybrid constants (A_n); distribution rate constants for transferring the drug from one compartment to another according to compartmental analysis ($k_{x,y}$); half-life ($t_{1/2}$, λ_n = ln 2/λ_n); area under the plasma concentration-time curve from time zero to infinity (AUC); volume of the central compartment ($V_c = D/A_1 + A_2 + A_3$); volume of distribution during the elimination phase ($V = D/\text{AUC}\,\lambda_3$) and at steady state ($V_{ss} = D\,\text{AUMC}/\text{AUC}^2$), where AUMC is the area under the first moment curve; fraction of teicoplanin in the body present in the central compartment at any time during the postdistributive phase ($f_c^* = \lambda_3/k_{10}$); and total plasma clearance (CL = D/AUC).

Teicoplanin adsorption to urinary sediments. To demonstrate teicoplanin adsorption to urinary sediments, two experiments were made in addition to the kinetic study. In experiment 1, two rats were housed in separated metabolic cages; only one of them was given food (standard diet 4 RF 21; Charles River). The urine was collected for 24 h into glass containers into which 200 μl of a 5.05-mg/ml [^{14}C]teicoplanin aqueous solution had been placed at the beginning of the experiment. Both urine samples contained some sediment; one also contained traces of the standard diet. The samples were shaken. A known volume of each suspension was diluted to three different concentrations for the microbiological assay. The same diluted solutions were also counted by LSC. Another part of each suspension was centrifuged at 1,500 × g for 15 min. A known volume of each supernatant was assayed by the microbiological method and by LSC, as described above.

In experiment II, six urine samples from different rats were collected at different intervals after drug administration, during an investigation of recovery of [^{14}C]teicoplanin. The samples containing traces of standard diet were centrifuged, and the supernatant and the pellet were separated and weighed. The sediments were assayed by LSC by the method described above for tissues. The radioactivity was also measured in weighed samples of supernatant.

RESULTS

Plasma kinetics. Following intravenous administration of [^{14}C]teicoplanin, the mean profiles of total radioactivity and microbiological activity in plasma were found to be similar (Table 1 and Fig. 1), and a three-exponent decay of teicoplanin concentration was observed with both assays.

Table 2 reports the main pharmacokinetic parameters of teicoplanin, as calculated from radiochemical and microbiological assay data.

Recovery of teicoplanin. Most of the administered dose was excreted in the urine in the first 12 h (63.4% radioactivity and 41.0% microbiological activity). The cumulative recoveries of teicoplanin in urine 120 h after administration were 76.3% (radioactivity) and 47.1% (microbiological activity) of the dose (Table 3).

In feces the recovery of teicoplanin as total radioactivity was low (8.7%), and no antimicrobial activity was found (Table 3). Negligible amounts of radioactivity were found in the exhaled air.

The mean cumulative recovery of total ^{14}C in the excreta (urine and feces) 5 days after drug administration was 85.0% of the dose, and the residual radioactivity found in the animal carcasses was 11.1%.

Tissue distribution. Histograms showing the distribution of teicoplanin at the most representative times are given in Fig. 2a to d. At the time of the first killing, 15 min after administration, maximum ^{14}C concentrations were observed in all organs except the liver and gonads. Organs with the highest concentrations were the kidneys, trachea, lungs, and

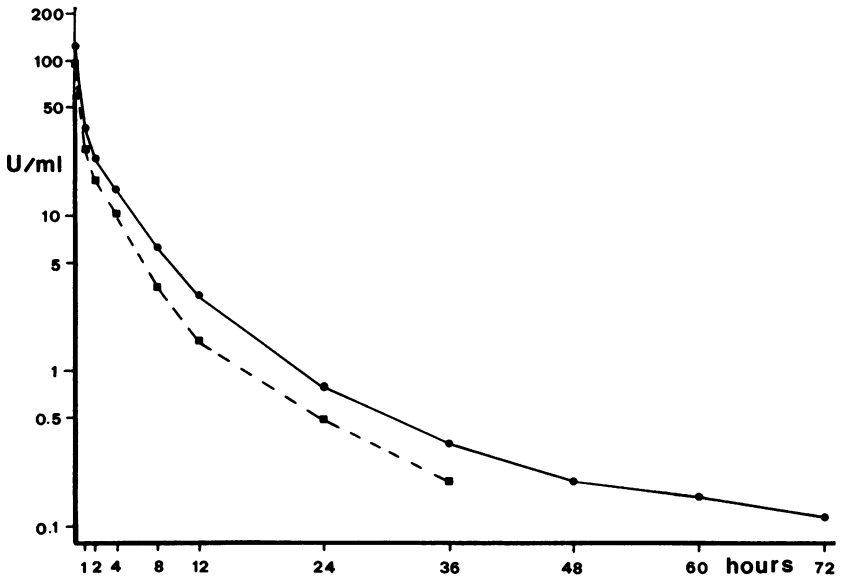

FIG. 1. Semilogarithmic plots of the mean teicoplanin concentrations in plasma versus time determined by radiochemical (●) or microbiological (■) assay.

adrenal glands. The lowest concentrations were observed in the brain, gonads, and eyes. Four hours after drug administration, ^{14}C levels increased in the liver and gonads to the maximum value, while it decreased in all other organs. The ratio of the ^{14}C level in tissue to plasma (K_p) became higher than 1.0 for trachea (2.0) and kidneys (1.6), while it was still below 1.0 for all the other organs. Twenty-four hours after drug administration, the ^{14}C concentration in all organs was lower than that at 4 h, and teicoplanin was no longer detectable in the brain. Concentrations in tissues declined at a slower rate than in plasma, and K_p values reached values of 27.4, 11.4, and 9.2 in the kidneys, adrenal glands, and liver, respectively. [^{14}C]teicoplanin was still detectable 120 h after drug administration, except in the brain and eyes. The disappearance of [^{14}C]teicoplanin from tissue was slower than from the plasma, resulting in a further increase of K_p values. Levels of [^{14}C]teicoplanin in blood, determined up to 24 h after administration, averaged 54.1 to 59.1% of the levels in plasma, suggesting that teicoplanin does not diffuse freely into erythrocytes.

TABLE 2. Pharmacokinetic parameters of teicoplanin calculated from plasma data obtained by microbiological and radiochemical assay[a]

Parameter	Mean ± SE (n = 4) determined by	
	Microbiological activity	Radioactivity
C_{max} (U/ml; 0.05 h)	95.6 ± 6.6	121.5 ± 4.6
$C_o = A_1 + A_2 + A_3$ (U/ml)	105.6 ± 7.7	
A_1 (U/ml)	69.6 ± 8.5	
A_2 (U/ml)	32.0 ± 3.1	
A_3 (U/ml)	3.9 ± 0.3	
λ_1 (h^{-1})	2.88 ± 0.11	
λ_2 (h^{-1})	0.38 ± 0.03	
λ_3 (h^{-1})	0.08 ± 0.00	0.03 ± 0.00
k_{12} (h^{-1})	1.17 ± 0.12	
k_{21} (h^{-1})	1.22 ± 0.09	
k_{13} (h^{-1})	0.17 ± 0.01	
k_{31} (h^{-1})	0.11 ± 0.01	
k_{10} (h^{-1})	0.68 ± 0.05	
V_c (liter/kg)	0.10 ± 0.01	
V (liter/kg)	0.72 ± 0.04	1.47 ± 0.07
V_{ss} (liter/kg)	0.28 ± 0.02	0.31 ± 0.01
AUC (U ml^{-1} h)	167.8 ± 2.2	247.9 ± 4.9
$t_{1/2}$, λ_1 (h)	0.24 ± 0.01	
$t_{1/2}$, λ_2 (h)	1.84 ± 0.11	
$t_{1/2}$, λ_3 (h)	8.49 ± 0.49	25.35 ± 0.80
f_c^* (%)	12.30 ± 0.97	
CL (ml/h per kg)	59.10 ± 0.77	40.04 ± 0.80

[a] Parameters are defined in the text.

Teicoplanin adsorption to urinary sediments. The results of teicoplanin adsorption to urinary sediments by experiment 1 (Table 4) and experiment 2 (Table 5) are shown. The presence of some sediment in urine, even when there was no dietary contamination, interfered with the microbiological

TABLE 3. Mean recovery of teicoplanin in urine and feces (n = 7) as total radioactivity and microbiological activity

Interval (h)	Recovery in urine by the following assay[a]:		Feces (^{14}C)[a]
	^{14}C	Microbiological	
0–12	63.4 ± 1.6	41.0 ± 2.8	
12–24	7.0 ± 0.8	3.9 ± 0.4	3.4 ± 0.8[b]
24–48	2.9 ± 0.5	1.5 ± 0.4	3.6 ± 1.2
48–72	1.1 ± 0.1	0.3 ± 0.0	1.0 ± 0.2
72–96	0.7 ± 0.1	0.2 ± 0.0	0.5 ± 0.1
96–120	0.6 ± 0.1	0.1 ± 0.0	0.2 ± 0.1
0–24	70.4 ± 1.3	44.9 ± 2.7	3.4 ± 0.8
0–120	76.3 ± 1.0[c]	47.1 ± 3.0	8.7 ± 1.3

[a] Values are expressed as percentages of the test dose and are means ± standard error.
[b] Value is for 0 to 24 h.
[c] With cage washing.

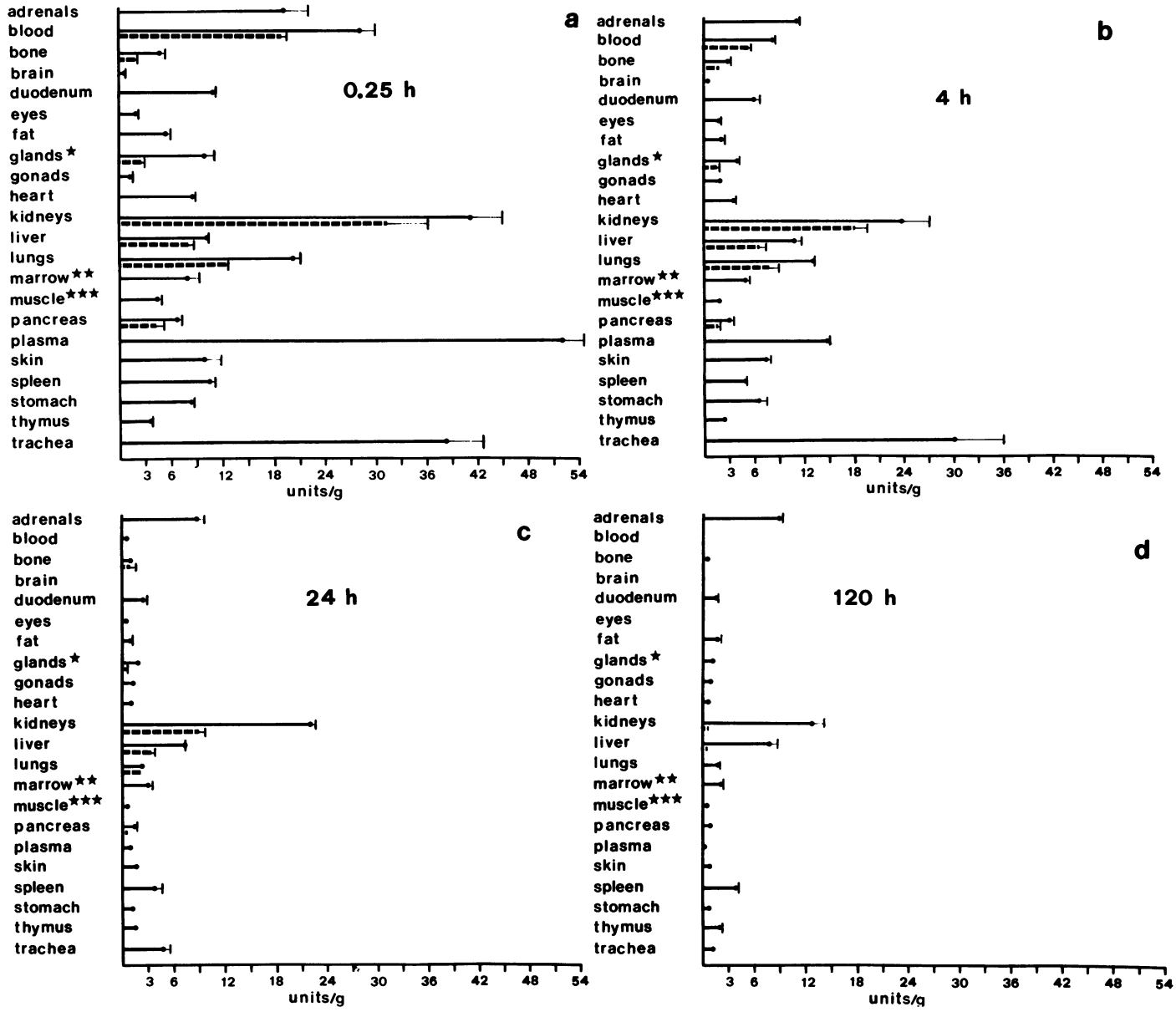

FIG. 2. Histograms showing the pattern of distribution of teicoplanin in rat organs and tissues (units per gram of wet tissue ± standard error) at 0.25 (a), 4 (b), 24 (c), and 120 (d) h after a single 10,000-U/kg intravenous dose. ——, Radiochemical assay; - - -, microbiological assay; *, salivary glands; **, bone marrow; ***, skeletal muscle.

assay, and this interference was enhanced by the presence of dietary residue. The lowest recovery of microbiological activity was found in the assay of suspended samples (experiment 1).

The radiochemical assay also detected teicoplanin bound to the sediment and dietary residue, and therefore both suspended samples gave a higher recovery of teicoplanin than the corresponding supernatants. Depending on the quality of the urine sample (i.e., coarseness of the sediments), the radiochemical assay measured the teicoplanin totally when it was bound to urinary sediment but only partially when it was bound to dietary residue (experiment 1).

The extent of teicoplanin adsorption to sediment in rat urine collected during the kinetic study was found to depend on the quality of the sample and even more on the teicoplanin concentration in urine. It was found that with a lower teicoplanin concentration the percentage of radioactivity bound to the sediment was higher (experiment 2).

DISCUSSION

After intravenous administration of [^{14}C]teicoplanin, the disposition of the antimicrobial activity in rats was consistent with a three-compartment model with elimination from the central compartment, as already observed for dogs (3) and humans (13, 14) and for vancomycin in humans (7). The distribution was biphasic and prolonged because the equilibria between the central compartment and the shallow and deep peripheral compartments were reached at different rates. The volume of distribution accounted for about 70% of the body weight, indicating a widespread distribution of

TABLE 4. Adsorption of teicoplanin to rat urinary sediments by experiment 1

Urine sample	Relative recovery of teicoplanin by:	
	Microbiological assay	Radiochemical assay
Without dietary residue		
Supernatant	100.00	100.00
Suspension	97.06	103.46
With dietary residue		
Supernatant	87.27	82.92
Suspension	68.41	89.12

teicoplanin into body fluids and tissues. In the postdistribution phase, 12% of the teicoplanin in the body was present in the central compartment.

The sensitivity of the radiochemical method was higher than that of the microbiological method, so that we could follow teicoplanin concentrations in plasma up to 72 h with the former method and only up to 36 h with the latter method. For this reason, the actual terminal half-life of teicoplanin calculated with microbiological data is probably underestimated.

An earlier investigation of the metabolites of teicoplanin in the 0 to 24 h urine sample of rats given the antibiotic intravenously showed that a negligible amount of teicoplanin (3 to 5% of the administered dose) undergoes chemical or metabolic transformation, and almost all teicoplanin is excreted unchanged (L. F. Zerilli, L. Cavenaghi, A. Bernareggi, and A. Assandri, manuscript in preparation). However, in the present study the level of urinary recovery of the administered teicoplanin determined by the microbiological assay was lower than that determined by the radiochemical assay (Table 3). The results of separate experiments (Table 4) indicated that the recovery of teicoplanin in urine, as determined by microbiological assay, could have been underestimated because of adsorption of teicoplanin to components of the urinary sediment, mainly to traces of the rat standard diet present in urine samples. Thus, some of the antibiotic would not be available for determination by the microbiological assay. The recovery of the administered dose in urine was assessed by assaying the samples after the sediments were suspended. In this way the radiochemical assay gave a more accurate determination of the dose excreted than the microbiological assay. The adsorption phenomenon was minimal for the urine samples that were collected in the first hours postadministration, that contained almost no dietary contamination, and that had high levels of teicoplanin; but it became important for the samples collected later. Thus, by using the radiochemical assay the cumulative recovery of the dose at 0 to 120 h may be only slightly underestimated because the largest part of the dose was excreted in the interval from 0 to 12 h.

TABLE 5. Adsorption of teicoplanin to rat urinary sediments by experiment 2

Teicoplanin concn (U/ml)	% Sediment[a]	Distribution (%) of radioactivity in:	
		Sediment	Supernatant
89.8	2.28	24.6	75.4
0.6	2.09	19.0	81.0
0.6	2.72	31.3	68.7
0.2	2.18	39.7	60.3
0.2	1.45	37.3	62.7
0.1	2.48	51.2	48.8

[a] (Weight of sediment/weight of supernatant) × 100.

A matrix effect that interferes in the microbiological determination of teicoplanin may explain why no antimicrobial activity was found in feces. In fact, when known quantities of teicoplanin were added to several dilutions of blank feces and assayed, the recovery of teicoplanin progressively decreased from 90% (dilution of 1/2,400) to 25% (dilution of 1/50).

A nonrenal mechanism of elimination also has been suggested for vancomycin (8) to explain the relatively high clearances of vancomycin observed in patients with compromised renal function (11).

The teicoplanin concentrations reached in the various organs and tissues were correlated with blood flow. The organs with the highest perfusion rates, lungs, kidneys, adrenal glands, liver, and heart, had the highest levels of teicoplanin. Because of the relatively high molecular weight (2) and the polarity of teicoplanin, the rate of distribution appeared to be limited by diffusion. The brain, which is a highly perfused organ and contains about 75% water but is clearly separated from the blood by a lipid barrier, contained only traces of teicoplanin. The lipid membrane of the erythrocytes seemed not to be crossed by teicoplanin, and fat contained only low concentrations of the antibiotic.

The affinity of teicoplanin for some components of the tissues, i.e., binding to structural tissue proteins, may further differentiate the extent of distribution in the various organs and may determine the slow release of teicoplanin from the tissue to plasma. The slow release appeared to be the rate-limiting step in the slow elimination of the antibiotic from the body (k_{10} was six times higher than k_{31}) and resulted in the relatively long terminal half-life of teicoplanin in plasma.

The liver (4%), kidneys (1.2%), skin (1.7%), and fat (1.2%) had the highest percentages of the residual dose in the animals' carcasses 5 days after the administration and, with the adrenal glands and spleen, they made up the deep compartment.

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